## REMARKS

Reconsideration and allowance of pending claims 1-6 is respectfully requested.

Claim 1 has been amended to further define the subject matter deemed the invention. The amendment to claim 1 was submitted in a Supplemental Amendment submitted October 24, 2000, but the Office Action mailed November 7, 200 does not indicate that this Supplemental Amendment was entered. Applicants respectfully submit that no new matter has been added via this amendment to claim 1.

The specification has been amended to correct for typographical errors introduced during drafting of the original application and its subsequent translation into English. Applicants respectfully submit that no new matter has been introduced into the application as filed via these amendments to the specification.

Applicants recognize that the application is under final rejection, but respectfully submit that the amendments to the claims and specification place the application in condition for allowance and that no new issues regarding further searching have been raised via these amendments. Entry into the record is requested.

Filed herewith is a Form PTO 1449 listing two documents that were previously cited in this application, but not considered. Consideration of the documents and return of Form PTO 1449 with the Examiner's initials by each listed reference are respectfully requested.

Cited art reference ROTE LISTE 1997 "CYCLO-cell" discloses only an effervescent tablet containing cyclophosphamide, but not the presently claimed film-



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coated tablet, and is not considered to impair the patentability of the claimed invention.

Cited art reference ROTE LISTE 1998 "CYCLO-cell 50" discloses a film-coated cyclophosphamide tablet containing corn starch, but no lactose monohydrate as a filler. In addition, the document does not specify whether the corn starch used is preswollen or non-preswollen, and the exact composition of the tablet is not disclosed. Accordingly, the presently claimed invention is submitted to be patentable over this document.

Claims 1-4 were rejected under 35 USC § 103 as being unpatentable over U.S. Patent No. 5,905149 to Battistini et al. (hereinafter Battistini '149 ) in view of U.S. Patent No. 5,593,691 to Eugster et al. (hereinafter Eugster '691). The Examiner asserts that because cyclophosphamide may be administered in a hypothetical combination with tyrosine kinase inhibitors, Battistini '149 somehow teaches the claimed film-coated tablet with cyclophosphamide as the active compound. Applicants traverse this rejection for at least the following reasons.

Tablet formation at the time the invention was made typically was accomplished using three basic methods, namely wet granulation, dry granulation, and direct compression. Direct compression was the most efficient process for commercial production of tablets, but few pharmaceutical substances are capable of undergoing direct compression into tablets without prior granulation, due to lack of cohesive strength. Binders, therefore, are mixed with active compounds to create a composition that is suitable for direct compression. Cyclophosphamide is one such active compound that is a poor candidate for direct compression. However, preparation of cyclophosphamide into tablets via granulation is less than satisfactory, due to problems with decreased dissolution rate over time. EP 519 099 teaches the

use of pregelatinized starch for preparing a stable pharmaceutical composition of cyclophosphamide that can be directly compressed into tablet form. The moisture in the pregelatinized starch used in EP 519 099 was disclosed as being key to improved stability of the cyclophosphamide subjected to direct compression. Pages 1-4 of EP 519 099 are enclosed herewith for the convenience of the Examiner.

An object of the claimed invention is to provide an oral cyclophosphamide formulation that avoids the process problems associated with press coated tablet formation using preswollen starch. *See* instant specification at page 1. At the time the invention was made, the state of the art required preswollen (gelatinized) starch be compounded with cylcophosphamide in order to achieve stability. The claimed invention, contrary to the mindset of the state of the art, provides a film-coated tablet comprising a core cyclophosphamide containing a dry binder exclusive of preswollen starch. As shown in Example 1, the claimed invention provides a surprisingly stable formulation. *See* instant specification at page 2.

Battistini '149 discloses a new class of tyrosine kinase inhibitors that may be administered as a mixture with one or more compounds recited in a laundry list of known antineoplastic agents. Cyclophos-phamide is merely one member of this list. Cyclophosphamide is known to be available when dosed in both oral and parental routes, but Battistini '149 fails to teach that one method of administration is preferable over another. Battistini '149 is silent with respect to formulations capable of providing stable sources of cyclophosphamide. No examples are provided of tablets containing cyclophosphamide, nor is there any teaching that would suggest the claimed invention, a film-coated tablet with cyclophosphamide as active compound, comprising in the core cyclophosphamide, one or more fillers, flow regulators, lubricants, and one or more dry binders, exclusive of preswollen starch.



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To the contrary, Battistini '149 expressly teaches that preswollen starch is an acceptable binder. The cornstarch described in Example 17 of Battistini '149 is a preswollen corn starch: "corn starch (10g) is suspended in warm water (90 ml) and the resulting paste is used to granulate the powder" (col. 18, lines 47-49). Therefore, Battistini '149 teaches away from the claimed invention.

The Examiner cites Eugster '691 to overcome the deficiencies of Battistini '149. Eugster '691 teaches new biotenside esters for use in the preparation of spontaneously dispersible concentrates containing therapeutic or cosmetically active substances (col. 1, lines 7-10). Eugster '691 teaches that cyclophosphamide may be combined with these esters. *See* Eugster '691 at column 11, lines 55-56. Eugster '691 also teaches that the sterol etsers disclosed therein may be incorporated into conventional pharmaceutical preparations, together with customary excipients and/or diluents and stabilizers. According to Battistini '149, customary stabilizers for cyclophosphamide are pregelatinized starches. Consequently, it is respectfully submitted that Eugster '691 does not remedy the deficiency of Battistini '149 to teach the present invention. No motivation is provided by either reference to modify the hypothetical tyrosine kinase/cyclophosphamide compositions of Battistini '149 to comprise the claimed binders exclusive of preswollen starch. Thus, Battistini '149 in combination with Eugster '691 neither suggests nor renders obvious the claimed invention. Reconsideration and withdrawal of the rejection are respectfully requested.



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In view of the foregoing amendments and remarks, Applicants respectfully submit that the application is in condition for allowance. Notification to that effect is respectfully requested. Should any questions relating to patentability remain, the Examiner is invited to telephone the undersigned to discuss the same.

Respectfully submitted,

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## APPENDIX
## MARK UP VERSION SHOWING CHANGES MADE

**IN THE SPECIFICATION:**

The specification has been amended as indicated below.

Page 1, paragraphs 2, 3 and 5 have been amended as follows.

Cyclophosphamide is an agent having a broad antitumor spectrum which has been [introduced [sic]] used in chemotherapy for decades for the treatment of solid tumors such as mastocarcinoma, bronchial carcinoma and hemoblastoses.

Until now, [on [sic]] known pharmaceutical forms of cyclophosphamide have been tablets, coated tablets and mainly lyophilizates with various auxiliaries such as mannitol or urea.

The need thus exists for a simple and economical preparation of a solid pharmaceutical formulation [form [sic]] comprising cyclophosphamide for oral administration. It is necessary to take into consideration here that the pharmaceutical forms have to be coated in order that direct contact with the cytotoxic active compound is avoided.

Page 2, paragraphs 2 and 5 have been amended as follows.

Suitable auxiliaries were selected on the basis of the compatibility investigations mentioned in Example I [[sic]]. It was surprising in this context that the



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stability of cyclophosphamide is somewhat indifferent in the presence of preswollen starch.

53.5 mg of cyclophosphamide and 86.5 mg of an [()auxiliary 1-10[) [sic]] or 3.0 mg of an [()auxiliary 11-18[) [sic]] were in each case mixed and compressed. The pressed tablets were stored at 31°C for 6 months. The assessment of decomposition of the active compound was carried out [[sic]] by means of chloride determination.

Page 4, paragraph 4 has been amended as follows.

11.83 g of polyethylene glycol and 2.37 g of polysorbate 80 are dissolved in 75.21 g of water. 1.9 g of carboxymethylcellulose sodium are dissolved in 80.0 g of water. The solutions are brought together. 23.67 g of talc, 23.67 g of titanium dioxide and 0.24 g of simethicone [simeticone [sic]] are then added and the mixture is homogenized. 17.73 g of a 30% strength ethyl acrylate/methyl methacrylate [metharcrylate [sic]] copolymer dispersion in water are then added. The tablet cores are then sprayed with the prepared suspension in a suitable apparatus:

**IN THE CLAIMS:**

The claims have been amended as indicated below.

1. (Twice amended) A film-coated tablet with cyclophosphamide as active compound, comprising in the core cyclophosphamide, one or more fillers, one or more flow regulators, one or more lubricants, and one or more dry binders, wherein



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at least one of the fillers is lactose monohydrate and [but] no preswollen starch is present as a dry binder.



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(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 519 099 A1**

# (12) EUROPEAN PATENT APPLICATION

(21) Application number: **91110086.5**

(51) Int. Cl.[5]: **A61K 31/675**, A61K 9/20

(22) Date of filing: **19.06.91**

(43) Date of publication of application:
**23.12.92 Bulletin 92/52**

(84) Designated Contracting States:
**AT BE CH DE DK ES FR GB GR IT LI LU NL SE**

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## (54) Direct compression cyclophosphamide tablet.

(57) A directly compressible pharmaceutical composition comprising cyclophosphamide and a partially or fully pregelatinized starch is disclosed. The pharmaceutical composition, when directly compressed into a tablet, exhibits unexpected stability when compared to cyclophosphamide in combination with other direct compression vehicles.

EP 0 519 099 A1

## Field of th Invention

This invention relates to a novel pharmaceutical composition. More particularly, this invention relates to an unexpectedly stable pharmaceutical composition comprising cyclophosphamide and a partially or fully pregelatinized starch, which composition can be directly compressed to form a pharmaceutical tablet.

## Background of the Invention

The compressed tablet is one of the oldest and most popular unit dosage forms for medicinal substances. The tablet as a dosage form can be traced to well over 1,000 years ago when a procedure for molding solid forms containing medicinal ingredients was recorded. As a result of the introduction of new carriers and compression vehicles, tablets are replacing many forms of pills, powders and capsules. Accordingly, tablets presently represent the largest production volume of all pharmaceuticals.

The reasons for the widespread use of tablets are apparent, since tablets facilitate: (1) administration of medication in an accurate dose; (2) fast and accurate dispensing with less chance of error and contamination; (3) ease of administration; (4) administration in a form in which the time and area of contact between the active ingredient and the taste buds are reduced, thus obviating the physiological problems associated with the oral administration of drugs that possess a bitter taste and, in the case of coated tablets, with drugs that possess a disagreeable odor; (5) release of drugs at specific locations in the gastro-intestinal tract to prevent degradation of drugs sensitive to the low pH environment in the stomach, prevent release of drugs that irritate the gastric mucosa in the stomach, and facilitate local action or preferential absorption at specific sites in the tract; (6) enhanced stability by effecting a marked reduction in the surface of the drug exposed to the environment; (7) rapid production; and (8) economy and ease in storage, packaging and shipping.

There are currently three basic methods for tableting. They are the wet granulation method, the dry granulation method and the direct compression (DC) method. The direct compression method is by far the desired method from the standpoint of processing time and requirements of equipment and materials. However, only a very limited number of pharmaceutical substances possess enough cohesive strength and flowability to allow direct compression without previous granulation. Certain crystalline materials, such as potassium bromide and potassium chloride can be compressed without preliminary treatment. Also, drugs such as aspirin and phenolphthaline can be directly compressed after blending with suitable tableting excipients.

It has been estimated that about 20 percent of the materials used for tableting in the pharmaceutical field may be compressed directly. In order to use this method to a greater extent, many more materials are modified either by treating the material in some special way during early stages of preparation, or by adding a direct compression vehicle, i.e., a dry binder or excipient material which will mix with the active ingredient to provide a flowable powder and form an easily compressible carrier. Exemplary United States patents relating to directly compressible tablets include 3,584,114 to Cavalli, et al., 3,725,556 to Hanssen, et al., 3,873,694 to Kanig, 4,072,535 to Short, and 4,439,453 to Vogel.

There are currently several available binders or excipients which can be used as direct compression vehicles. They include spray-dried lactose; anhydrous lactose; microcrystalline cellulose; dicalcium phosphate dihydrate, unmilled; spray-congealed mannitol; ungelatinized starch (e.g., corn starch), and partially or fully pregelatinized starch.

Starch, as defined by the National Formulary XVI, "consists of the granules separated from the mature grain of corn {Zea mays Linne (Fam.Gramineae)} or of wheat {Triticum asetivum Linne (Fam.Gramineae)}, or from tubers of the potato {Solanum tuberosum Linne (Fam.Solanaceae)}." Pregelatinized starch is defined by the National Formulary XVI as "starch that has been chemically and/or mechanically processed to rupture all or part of the granules in the presence of water and subsequently dried. Some types of pregelatinized starch may be modified to render them compressible and flowable in character." Many types of partially or fully pregelatinized starches are commercially available for use in direct compression tablet formulations.

With the advent of the above described direct compression vehicles, drug manufacturers are seeking to formulate or reformulate pharmaceutically active compounds into compositions which are directly compressible into tablets. One such compound is cyclophosphamide, an anti-neoplastic agent manufactured by Bristol-Myers Company under the trademark CYTOXAN®, which is currently tableted with specially prepared directly compressible diluent. This DC diluent is produced by a wet granulation process. However, processing cyclophosphamid using wet granulation method has certain drawbacks. A major problem is that it is difficult to control the moisture of the resulting tablet. A second problem is that the dissolution rate, i.e.,

the rate at which th tablet dissolves in water, decreases over time. The third problem is that the dissolution rate of th tablet varies from batch to batch, with som batches having unacceptably low rates.

Obviously, a direct compression cyclophosphamide tablet would be desirable. Unfortunately, cyclophosphamide is not one of the few known compounds which possesses th cohesive strength and flowability to allow direct compression. Thus, there is a need for a directly compressible composition comprising cyclophosphamide and a direct compression vehicle, which composition obviates the problems resultant from wet processing.

Accordingly, it is an object of this invention to provide a directly compressible pharmaceutical composition comprising cyclophosphamide and a direction compression vehicle.

## Summary of the Invention

Surprisingly, a directly compressible pharmaceutical composition has been discovered comprising cyclophosphamide and a partially or fully pregelatinized starch. It has been found that this composition, when directly compressed into a tablet, exhibits unexpected and remarkable stability when compared to CYTOXAN tablets or cyclophosphamide in combination with other directly compressible vehicles.

## Brief Description of the Drawing

Figure 1 is a schematic diagram of a process for making a direct compression cyclophosphamide tablet in accordance with this invention.

## Detailed Description of the Invention

Cyclophosphamide is listed as a cytotoxic agent by the Environmental Protection Agency. Accordingly, a "core tablet blend" containing the cyclophosphamide is first prepared and compressed to form a compressed core tablet. The compressed core tablet is then covered or encapsulated by a second compressed coating called a "press coat blend", which contains no active ingredients. Thus, persons handling the tablets do not directly contact the carcinogenic cyclophosphamide.

### I. THE CORE TABLET BLEND

The core tablet blend in accordance with this invention comprises a mixture of cyclophosphamide, a partially or fully pregelatinized starch, and optionally, additional diluents or other ingredients such as disintegrants, lubricants, glidants, etc.

#### A. The Cyclophosphamide and Pregelatinized Starch

The cyclophosphamide used in this invention is the crystalline monohydrate form. For purposes of the procedures described below, it is preferred that the particle size be approximately 40 mesh or smaller. Due to its low melting point (46 ° C), cyclophosphamide is not conducive to milling. When orally administered, cyclophosphamide is usually prescribed in dosages of 25 mg, 50 mg, or 100 mg.

Several different types of partially or fully pregelatinized starch (hereinafter simply "pregelatinized starch") can be used in accordance with this invention. The pregelatinized starch should meet all National Formulary XVI standards and be capable of mixing with cyclophosphamide to form a directly compressible tablet. Those skilled in the art can by simple routine experimentation determine those starches capable of forming direct compression tablets with cyclophosphamide, and the optimum mixtures for doing so.

Commercially available pregelatinized starches which can be used include STARCH 1500 (formerly STA-RX 1500), which is a modified, partially gelatinized corn starch produced by Colorcon, Inc., West Point, Pennsylvania; several pregelatinized starches produced by the Hubinger Company, Keokuk, Iowa, including CERI-GEL 300, a five percent modified, fully pregelatinized corn starch, CERI-GEL 433, which is a modified, fully pregelatinized corn starch, PREGEL, which is an unmodified, fully pregelatinized corn starch, INSTANT KEOGEL, which is a 100 percent modified, fully pregelatinized corn starch, and TENDER JEL, which is a 100 percent modified, fully pregelatinized corn starch; WHEATGEL 100, which is a fully pregelatinized wheat starch produced by International Grain Products, Montreal, Canada; and several pregelatinized starches produced by the A.E. Staley Manufacturing Company, Hulton, Maine, including BINASOL 15, which is a modified, fully pregelatinized tapioca starch, BINASOL 81, which is a modified, fully pregelatiniz-

starch, and STA-RX, which is a modified, fully pregelatinized corn starch.

It has been found that STARCH 1500 provides the best results, but that the other pregelatinized starches mentioned above will also provide good results. STARCH 1500 is a modified, partially pregelatinized corn starch containing approximately 5 percent amylose, 15 percent amylopectin, and 80 percent unmodified corn starch. STARCH 1500 has a cold water soluble fraction of 10-20 percent.

All starches contain two types of carbohydrate chains, i.e., amylose and amylopectin, which both have the same basic chemical structure. However, they are slightly different, which accounts for their very different individual properties. Amylose has a straight chain molecular make-up, while the amylopectin has a multi-branched make-up. In unmodified corn starch, amylose and amylopectin are randomly mixed throughout the starch grains and are held together by hydrogen bonding that prevents them from functioning independently. The gelatinized process breaks that hydrogen bonding and allows the two chains to function separately.

STARCH 1500, when used as a capsule excipient for aspirin, is known to provide better stability than either anhydrous lactose or microcrystalline cellulose excipients. It is also known that aspirin is an ester that easily undergoes hydrolysis in the solid state when exposed to ambient moisture. STARCH 1500 has a high moisture content; however, this moisture is apparently not available to hydrolyze the aspirin molecule. In contrast, degradation of cyclophosphamide (CY) monohydrate in solid dose forms is initiated by dehydration resulting in the loss of CY monohydrate crystalline structure. CY monohydrate degrades rapidly when the moisture content is less than the monohydrate equivalent. Without being bound by theory, the improved stability is believed to be due to the moisture of STARCH 1500 maintaining the CY in its monohydrate state. This is surprising and unexpected since the moisture is tightly bound and essentially unavailable as indicated by the stability of aspirin in the presence of STARCH 1500.

The pregelatinized starch can be dried prior to mixing with cyclophosphamide. However, no significant differences have been observed using dried pregelatinized starches versus using undried pregelatinized starches.

Using STARCH 1500, it has been found that a cyclophosphamide/pregelatinized starch ratio of approximately 2:1 provides an adequate blend compatibility to produce core tablets that can be transferred intact for compression coating on a tablet press. Such a blend is advantageous because it is predominantly cyclophosphamide, resulting in a smaller, more easily swallowable tablet.

B. Additional Diluents

Optionally, other direct compression vehicles can be added to the core tablet blend. However, such diluents are not necessary because a core tablet blend of cyclophosphamide and pregelatinized starch is usually sufficiently compressible to provide an acceptable compressed core tablet. Moreover, the presence of other diluents might have a detrimental effect on stability. Other diluents include lactose monohydrate, microcrystalline cellulose, calcium phosphate (dibasic, milled), ungelatinized corn starch, and dextrates.

C. Disintegrants

Disintegrants are substances that are added to the ingredients of a pharmaceutical tablet to facilitate its disintegration in the presence of water or biological fluids, and thus hasten the release of the active ingredients. In experiments with the core tablet blend of this invention, sodium starch glycolate was used to facilitate disintegration. Experiments in which the level of disintegrant was 0.0 percent, 4.0 percent and 8.0 percent were carried out to evaluate the effects on tablet dissolution, disintegration, hardness, durability and weight variation. The test results indicated that increasing or decreasing the disintegrant level had no adverse effect on the physical attributes of the tablet. Even though the test results indicated that a disintegrant is unnecessary, it is preferred to include sodium starch glycolate at a 4.0 percent level to assure disintegration and performance of aged tablets or tablets made with different batches of excipients.

D. Lubricants

Lubricants are ingredients that can be added to a tablet blend to facilitate ejection of the tablets from the dies after compression and to prevent tablets from sticking to the punch faces. Acceptable tablets can be manufactured using magnesium stearate in concentrations of 0.25 percent, 0.5 percent and 1.0 percent of the tablet weight, with no tablet picking or sticking to the punch faces. However, a 1.0 percent concentration has a detrimental effect on tablet durability and maximum achievable hardness. Prolonged mixing of the powder blend containing 0.5 percent does not significantly effect the dissolution characteris-